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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/824,587	04/03/2001	Lorraine D. Butlin	IMIN.P-032	8700

21121 7590 07/22/2005

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EXAMINER	
NGUYEN, BAO THUY L	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/824,587	BUTLIN ET AL.	
	Examiner	Art Unit	
	Bao-Thuy L. Nguyen	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 18 May 2005 has been entered.

2. Claims 21-50 are pending.

Claim Rejections - 35 USC § 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It appears that applicant is not claiming the invention that applicant believes is claimed.

The preamble of claim 21 states that a method for differentiating between a first state and a second state of an analyte is being claimed. Where the first and second state

are defined as different because they (i.e, the sample) contain different amounts of the same forms or isoforms of the analyte.

However, it does not appear that claim 21 accomplishes this goal. Applicant argues that a method for differentiating between different forms or isoforms is not being claimed. Instead, the relative amount of each form in a sample is being sought and detected (see arguments submitted 5/18/05, page 9.) It is unclear how this is accomplished in claim 21. This claim requires that two assays be performed on aliquots of a single sample using the same pair of analyte-specific binding agents. Presumably, the results from these two assays (regardless of how they are performed) should be the same. In a previous submission (6/20/2004, paragraph bridging pages 8 and 9), applicant argues that although the reagents in the two assays are the same and the samples are the same, the amount of reagent captured in the two assay methodologies is quite different. This is not understood. No proof is offered to support this statement, thus it cannot be seen how the same reagents can be used on the same sample to detect the same analyte in two sandwich assays can offer different results.

Regardless, claim 21 furthers states in step (e): comparing the amount of first binding agent/analyte/second binding agent complex formed in the first specific binding assay and the second specific binding assay. This has been interpreted to mean that the result from the first specific binding assay is compared to the result from the second specific binding assay and that this comparison can be expressed in a ratio.

Since it would be expected for the results from the first and second specific binding assay to be the same, this ratio should be 1 when expressed in numerical value.

Claim 21 also states that at least one of the first and second binding agents has a different specificity for the forms of the analyte. This is understood to mean that either the first or second binding agent binds to a different form of the analyte in each of the two assays (i.e. they have different specificity for each form of the analyte that may be in the sample). In which case, this is a method of differentiating between different forms of the same analyte in a sample. This, then, is contradictory to applicant's arguments and to the preamble.

Furthermore, the statement that the same pair of analyte specific binding agent is used in both assays is confusing since they are also recited as having different specificity for the different forms of the analyte. If the same pair of binding agent is used on the same sample, regardless of which form it is specific for, the results should be the same. On the other hand, if the binding agents have different specificity for different forms of the analyte, and the results of the two assays are different, it can be deducted that the binding agents in the two assays are not the same.

Page 3, lines 10-14 of the specification states that at least one member of said pair of binding agents having a different specificity for each of said two states of said analyte, and the first test signal is compared to the second test signal. And Page 4, lines 1-3, states that each member of said pair of binding agents has a different specificity for each said two states of said analyte. This would mean that each pair of antibody binds

to a different form of the same analyte and when a ratio is taken, it can be compared to a standard ratio for one or the other of the two states to determine in which state the sample analyte exists (specification, page 4, lines 11-16). This is completely different from what is being claimed in claim 21. Claim 21, essentially claims a comparison between the result of the first assay with the result of the second assay to differentiate between a first state and a second state.

Applicant argues on page 10, second paragraph that the amount of first binding agent/analyte/second binding agent complex formed in the first and second specific binding assays differs depending on the state of the analyte in the sample. It is unclear if this means that the amount of the analyte in the first assay is different from the amount of the same analyte in the second assay, or if it means that the amount of the analyte in the first and second assay is different from the amount in a standard ratio. If it is different from a standard ratio, the claim should be amended to clarify and to specifically and unambiguously claim the invention.

Claim Rejections - 35 USC § 112, first paragraph

4. Claims 21-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims have been amended to recite a method for differentiating between a first state and a second state of an analyte, wherein in the first state, the analyte is present in a first set of forms and in the second state the analyte is present in a second set of forms, where the first set of forms differs from the second set of forms as a result of containing different forms of the analyte in different relative amounts.

This is understood to mean the following: A method for differentiating between a first state and a second state of an analyte, wherein the first and second state are defined as different because they contain different relative amount of the same form of the analyte.

In the arguments submitted 20 June 2004, applicant states that they are not claiming the differentiation of different forms. Instead, the claims are drawn to "differentiating analyte *states* which may be the result of compositions having the same forms in differing relative amounts." Applicant also states that this is exactly what is shown in Example 3. And in the arguments submitted 18 May 2005, applicant submitted a diagram of the two states as illustrated by their relative amounts. Therefore, the above interpretation of the amended claim is consistent with the arguments submitted.

However, because of the confusion in the claims as detailed in the 112, 2nd paragraph rejection above, it is the position of the office that applicant does not have possession of the invention as claimed. The specification, indeed teach a method for performing a sequential and a "substantial simultaneous" assay on aliquots of the same

sample, or contemporaneous samples using the same pair of antibodies (i.e. Mabs 4813.2 and 4882.1), however, the specification does not teach that the results obtained from these two assays when compare to each other, differentiate between a first state and a second state of an analyte. Instead, the specification teaches that the results obtained are compared with a standard ratio.

Example 3 teaches the detection of FSH concentration in 8 consecutive daily urine samples from one fertile woman and 9 consecutive daily urine samples from one post-menopausal woman. FSH concentration in each sample is measured using the sequential and simultaneous assays. The results shown are indicative of different amounts of FSH in a pre-menopausal sample versus a post-menopausal sample, i.e. the ratio taken in one set of sample (or more accurately, in one pre-menopausal woman) is compared to the ratio taken in another set of sample (or more accurately, in one post-menopausal woman) and a differentiation between a pre and post menopausal condition is made. The results do not show that in one set of sample, for example, D14, a first state and a second state of FSH (i.e. different forms of FSH) is differentiated, such as claimed.

Nothing in the specification teaches one how to distinguish between the different forms (as defined on pages 1, 2 and 8 of the specification) of the analyte based on their amount in a set of sample; nor is there a teaching that the different forms of the analyte can be differentiated using the method of the invention.

Applicant argues that example 3 clearly shows that FSH can be shown to exist in two different states using the method of the instant invention. This argument is not persuasive. Example 3 shows that the differentiation is between two different subjects, e.g. the result of the test sample is compared to a standard ratio in order to determine in which state the analyte exists. This comparison is not taught in the claim. In claim 21, the comparison is made between the result obtain in the first assay and the result obtain in the second assay, both assays are performed on the same sample using the same pair of binding agent (as previously argued, the first binding agent in the first assay is the same as the first binding agent in the second assay, and the second binding agent in the second assay is the same with the second binding agent in the second assay, but the first and second binding agents are different from each other, see arguments submitted 11 January 2004, page 6, 4th paragraph). The specification does not teach this. The specification teaches that the result obtained is compared to a known standard.

Applicant argues that the claim requires that the analyte exists in at least two states that two tests are performed, on a sample, and that based on a comparison of these two tests one can tell the difference between the two choices for the state in which the analyte exists. Applicant also argues that the claims do not require the results in one set of sample, for example, D14, a first state and a second state is differentiated.

This argument is not persuasive. In this instant, the samples supposedly show 8 consecutive daily urine samples taken from one fertile woman and the analyte concentration in each sample was measured to the two step and one step assays,

therefore, D14 is seen to represent at least one of those 8 samples. In which case, the result shown for D14 is not compared to itself, rather it is compared to a standard, i.e. a sample taken from a post-menopausal woman. The claims do not teach this. Furthermore, although it may be true that the analyte exists in at least two states and that two tests are performed on a sample, the claim does not required that the two states of the analyte exist in each and every sample collected. According to the diagram on page 9 of the arguments, the sample could conceivable contain only one form of the analyte. Applicant argues repeatedly the that results obtained from the one-step and two-steps assays are compared to each other, however, it is unclear how this is done to satisfy the full intent of the claimed invention. The specification does not teach that the comparison of the results from the two assays to each other could lead to a determination of which state the analyte is in. Instead, the specification teaches that a ratio of the two assays is taken and compared to a known standard. Additionally, as stated above, if the same pair of binding agent is used in both assay, the results should be same regardless of its specificity toward the different forms of the analyte. Because in each assay, the same binding agent is used, therefore, they are expected to bind to the same analyte form, the amount of analyte detected may be different in different sets of samples, but they should not expected to be different in the same sample or aliquots of the same sample.

5. Claims 21-50 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for distinguishing between pre-menopausal and post-menopausal FSH in samples at different time intervals, does not reasonably provide enablement for a method for differentiating between a first state and a second state of an analyte in contemporaneous samples using the same reagents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification on page 9, lines 6-10 teaches the analysis of FSH samples using a pair of novel anti-FSH monoclonal antibodies that distinguish between pre-menopausal and post-menopausal FSH samples. The specification further teaches that for more accurate diagnosis of menopausal conditions the assay results should be determined numerically, and expressed as a ratio of the signals of the first and second assays. A significant change in this ratio can indicate transition from a pre-menopausal to a post-menopausal state, or vice-versa. Thus the results from a series of contemporaneous tests performed, for example, every few weeks, can be collated and any change in the observed signal ratio used to diagnose a change in condition. Page 11, lines 5-19.

The specification does not teach the method as claim in claim 21, mainly the performance of a one-step and two-step assays on contemporaneous samples from the

same source, or aliquots of the same sample, and comparing the results of these two assays to each other in order to differentiate between the different states of the analyte.

Response to Arguments

6. Applicant's arguments filed 18 May 2005 have been fully considered but they are not persuasive. All arguments are addressed above.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao-Thuy L. Nguyen whose telephone number is (571) 272-0824. The examiner can normally be reached on Tuesday and Thursday from 8:00 a.m. -3:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bao-Thuy L. Nguyen
Primary Examiner
Art Unit 1641
7/20/05